REMARKS

Claims 109-123 are currently pending in the application. The Examiner has made a number of objections and rejections that, for clarity, are listed below in the order in which they are addressed herein.

I. The priority claim to patents and applications prior to 30 August, 1995 is alleged to lack support;

II. Claims 110 and 123 are objected to for depending from a rejected base claim;

III. Claims 109, 111-115, 117, 118 stand rejected under 35 U.S.C. §102(e) as allegedly being unpatentable over Carrino, *et al.*;

IV. Claims 109,111 and 117-122 stand rejected under 35 U.S.C. §102(e) as allegedly being unpatentable over Griffin, *et al.*;

V. Claim 116 is rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement.

I. Priority Claim

The Examiner asserts that the instant claims are not supported by applications in the priority chain prior to Appl. Ser. No. 08/520,946, filed on 30 August, 1995 (Office Action page2). Applicants respectfully disagree. The present application claims priority to, *inter alia,* Appln. Ser. No. 08/484,956, filed June 7, 1995, Appln. Ser. No. 08/402,601, filed March 9, 1995, Appln. Ser. No.08/337,164, filed November 9, 1994, and Appln. Ser. No.08/254,359, filed June 6, 1994. Applicants submit that support for the instant claims is found at least as early as priority Appln. Ser. No.08/254,359, filed June 6, 1994, now issued as U.S. Patent No. 5,614,402, and in the specifications of each of the intervening cases.

The instant claims relate to kits comprising a cleavage means and a first oligonucleotide comprising a duplex region adjacent to a single-stranded 3' arm, wherein said first oligonucleotide comprises a fluorophore having quenched emission. Cleavage means are disclosed in each and every priority application (*e.g.*, the '402 patent is entitled "5' Nucleases Derived From Thermostable DNA Polymerase"). Oligonucleotides comprising a duplex region

adjacent to a single-stranded 3' arm are disclosed, *e.g.*, in the '402 patent in Part Two of Figure 1B, Figure 6, 19A, 20A and 20B. Figure 1B further diagrams a second oligonucleotide comprising a region that is complementary to the single-stranded 3' arm of the first oligonucleotide (see, *e.g.*, Part 1 of Figure 1B), a third oligonucleotide, and a nucleic acid molecule to which a portion of the second oligonucleotide and the third oligonucleotide are complementary, as recited in Claims 119-123. These figures in the priority specifications are the same as those included in the present application, and having the same numbering.

Each specification further describes embodiments using oligonucleotides that are labeled with fluorophores having quenched emissions. For example, Figure 27 is the same in each specification and shows a schematic representation of an increase in fluorescence when a fluorophore is separated from a quenching moiety (*e.g.*, a second fluorophore) upon cleavage of the oligonucleotide by a 5' nuclease. Such an embodiment is described in Example 8, also present in each specification, which recites, "In this embodiment, the oligo contains two fluorescein labels whose proximity on the oligo causes their emission to be quenched." See, *e.g.*, page 140, lines 6-8 of the instant specification and col. 46, lines 23-25 of the '402 patent.

For the reasons recited above, Applicants submit that the instant claims find support in the priority applications at least as early as the June 6, 1994 filing date of Appln. Ser. No. 08/254,359.

II. Claims 110 and 123 are objected to for depending from a rejected base claim. The Examiner has indicated that these claims would be allowable if rewritten in independent form and containing all the limitations of the base claim and any intervening claims (Office Action, page 2).

As explained further below, without acquiescing to the Examiner's arguments, by the present amendment Claim 110 is rewritten in independent form containing all of the limitations of base claim 109. Claim 123 depends from rejected Claim 122, which now depends (via Claims 119 and 121) from Claim 110. As each of these claims contains all of the limitation of new base Claim 110, Applicants submit that the claim from which Claim 123 depends is allowable, and respectfully requests that this objection be removed.

III-IV. Claims 109, 111-115, 117, and 118 stand rejected under 35 U.S.C. §102(e) as allegedly being unpatentable over Carrino, *et al.*, while Claims 109, 111 and 117-122 stand rejected under 35 U.S.C. §102(e) as allegedly being unpatentable over Griffin, *et al.* The Examiner has admitted, however, that Claim 110 is not anticipated by these references (Office Action page 2). While Applicants respectfully disagree that that Claim 109 and claims depending therefrom are anticipated by these references, for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Applicants by the present amendment have rewritten Claim 110 in independent form containing all of the limitations of Claim 109. The remaining claims as amended depend from Claim 110 and contain all the limitations thereof. Applicants therefore submit that the instant claims are not anticipated by either Carrino or Griffin and respectfully request that these rejections be withdrawn.

V. Claim 116 is rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. In particular, the Examiner asserts that the subject matter is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time of the invention, had possession of the claimed invention. The Examiner in particular asserts that the specification does not fully describe modification of a thermostable DNA polymerase to have reduced synthetic activity. Applicants respectfully disagree.

Applicants teach that DNA polymerases from thermophilic eubacteria share extensive protein sequence identity and that these polymerases behave similarly in both polymerization and nuclease assays (Specification at page 113, lines 1-4). Applicants selected DNA polymerases from *Thermus aquaticus* (*Taq*) and *Thermus flavus* (*Tfl*) as representative members of the class of thermostable DNA polymerases and teach how to obtain modified *Taq* and *Tfl* DNA polymerases that have reduced synthesis (*i.e.*, polymerization) activity, yet retain substantially the same 5' nuclease activity of the parent DNA polymerase (Example 2 at pp. 112-130).

The specification teaches that the 5' nuclease activity of eubacterial type A DNA polymerases is found in the one-third N-terminal region of the polymerase and that the polymerization domain is found in the C-terminal two-thirds of the protein (p. 40, lines 9-14).

The specification details strategies for obtaining the desired synthesis-deficient DNA polymerases at pages 47-52 and in Ex. 2. Figures 4 and 5 provide schematics showing the location of regions in the native *Taq* and *Tfl* DNA polymerases important for synthetic ability. The specification further provides the variant enzymes detailed in these figures and demonstrates their function (see, *e.g.*, Examples 3 and 5, starting at pages 131 and 134, respectively). Thus, the specification provides adequate guidance as to which regions of thermostable eubacterial polymerase genes can be targeted to generate mutations which reduce or abolish synthetic activity.

Nonetheless, for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Applicant herein cancel Claim 116, rendering this rejection moot.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all outstanding issues have been addressed and that Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

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By: _____

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